REMARKS/ARGUMENTS

Claims 1-4, 6-24 and 26-40 are pending. Claims 1, 6, 7, 12, 21, 33 and 34 have been amended herein. As set forth more fully below, reconsideration and withdrawal of the Examiner's rejections of the claims are respectfully requested.

Claim Rejections Under 35 U.S.C. § 102

The Examiner has rejected Claims 1, 2 and 10 as anticipated by LaHann. LaHannn teaches a pharmaceutical composition comprising propoxyphene and methylcellulose. Applicants have amended Claim 1 to remove the recitation of propoxyphene.

The Examiner has rejected Claims 1, 10 and 11 as anticipated by Merrill et al. Merrill et al teaches pharmaceutical compositions comprising analgesics and carboxymethyl cellulose. Applicants have amended Claim 1 to remove the recitation of carboxymethyl cellulose.

Applicants therefore respectfully request the Examiner's rejections under 35 U.S.C. § 102(b) be withdrawn.

Claim Rejections Under 35 U.S.C. § 103

A. Rejections over Lazarus and drugs.com web site.

The Examiner continues to reject Claims 1, 8-12, 16-19, 21, 28-30, 33 and 37-39 under 35 U.S.C. § 103(a) as being obvious over Lazarus, H. et al., A Multi-Investigator Clinical Evaluation of Oral Controlled-Release Morphine (MS Contin® Tablets), Hospice Journal, 6(4):1-15 (1990) (hereinafter "Lazarus") and the description of Senokot-S® tablets from the drugs.com website.

Applicant's Arguments are Commensurate in Scope with Claim Limitations

Initially, the Examiner argues that Applicants' arguments over Lazarus are not commensurate in scope with the limitations of the presently pending claims. Specifically, the Examiner argues that the pending claims do not "require administration of a pharmaceutical composition wherein the increase of the dosage range of the stool softener, namely docusate, corresponds to a linear increase [ ] of the dosage [ ] of the analgesic." Applicants respectfully

disagree. All of the pending claims, including Claims 1-4 and 6-20 drawn to a pharmaceutical composition and Claims 21-24 and 26-40 drawn to methods of using the compositions, all require the production or use of a pharmaceutical composition containing an analgesic and a stool softener.

With respect to the composition claims, Applicants submit that the claims specified "a pharmaceutical composition" and were therefore inherently directed to a single oral dosage form containing the recited ingredients. Applicants have amended Claim 1 to specifically state that the claimed pharmaceutical composition is formulated as a single oral dosage form. Further, Applicants note that this limitation also appears in the pending method claims. Applicants submit that the pending claims, as amended, are drawn to a single oral dosage form containing an analgesic and a stool softener and methods of using the same.

Applicants further submit that it is apparent to one of skill in the art that a single oral dosage formulation cannot be used to separately titrate the active ingredients contained in the formulation. Thus, it does not matter whether the formulation is a solid tablet or an oral liquid, or whether it contains 10 mg of stool softener or 300mg of stool softener or whether it contains 10mg of an analgesic or 2000mg of an analgesic; use of the single dosage form to double the dose of one of the ingredients inherently requires doubling the dosage of the other ingredients present in the dosage form. There is no way to separately titrate the different ingredients within the same dosage form - if the dose of one ingredient is doubled (by the administration of two of the dosage forms) or tripled (by the administration of three of the dosage forms) or quadrupled (by the administration of four of the dosage forms) or cut in half (by the administration of one-half of the dosage form) the dose of the other ingredients present must also follow the dosage increase or decrease by the same factor. Thus, Applicants submit that, contrary to the Examiner's arguments, the presently claimed pharmaceutical composition does require a linear increase in the administered dose of any individual ingredient when the dosage form is used to increase the dosage of one of the other ingredients.

Lazarus Teaches Away from the Formulation and Use of a Single Oral Dosage Form

In response to Applicants' previous arguments that Lazarus teaches away from the formulation and use of the presently claimed pharmaceutical compositions, the Examiner argues that Applicants have misconstrued the data and teachings of Lazarus.

Lazarus conducted a study of quality of life of cancer patients experiencing moderate or severe pain treated with an oral controlled-release morphine preparation (see Lazarus, page 11, first full paragraph). The investigators found that the patients treated were previously under-medicated with respect to analgesics and therefore required a substantial increase in analgesic administration to titrate to adequate pain control. For this reason, the investigators concluded that increased analgesic dosage was necessary to achieve only mild pain in these patients thereby improving their quality of life scores, although it was unclear whether this improvement was due to increased analgesic or to the administration of a controlled-release oral morphine composition (see Lazarus, page 12, second paragraph).

In addition to titrating the dose of oral controlled-release morphine to improve the quality of life, the investigators also studied aggressive use of laxative and antiemetic therapy concurrently with the titration of the analgesic. Because they did not separately analyze the effects of these additional treatments, the investigators could not draw distinct conclusions about the efficacy of each of these therapies other than to state that the role of SKS in alleviating adverse reactions to the oral morphine composition was "thought to be important" (see Lazarus, page 13, first paragraph). Despite these limitations in the study method, the investigators do draw the conclusion that "less frequent dosing with MSC, combined with the proper dose titration, plus the aggressive use of laxatives, resulted in a global improvement of quality of life for the patients involved in this study" (see Lazarus, page 13, second paragraph). While the investigators designed and conducted a study that made it difficult to separate positive effects of each variable investigated, they were able to conclude that aggressive laxative use combined with reduction in frequency of morphine dosing and simultaneous titration to proper dosing levels results in global improvement in quality of patient life. But, as noted by the investigators, and

presented in Figure 1, alleviation of the adverse effect of constipation required simultaneous titration of the dose of the two laxatives used and the dose of the oral morphine composition used. This separate titration of the laxative dose that resulted in the increased quality of patient life (that was the entire point and ultimate conclusion of the Lazarus article) was not linear. In fact, as the Examiner notes, the dosing of the laxatives was only modestly correlated ($r=0.51$) with the titrated morphine dose.

Figure 1 shows the number of SKS tablets taken associated with the morphine dose of the study patients. This figure shows that:

a. at a daily morphine dose of 60mg, the patients administered an average of 3 SKS tablets - that is, the patients administered 150mg docusate.

b. at the daily morphine dose between 60mg and 120mg of morphine, the patients still only administered 150mg of docusate - that is, as much as doubling the daily morphine dose was correlated with no increase in the dose of docusate.

c. at a daily morphine dose of 120mg to 180mg of morphine, the patients administered 200mg of docusate - that is, as much as tripling the daily morphine dose was correlated with increasing the dose of docusate by only one-third.

d. at a daily morphine dose of greater than 180mg of morphine, the patients administered 250mg of docusate - that is, more than tripling the daily morphine dose was correlated with increasing the dose of docusate by only two-thirds.

These were the titration steps of the increased morphine dose that led to the increased quality of life that was the beneficial conclusion identified by the study authors. According to the study authors, this benefit was bolstered by the aggressive prevention and treatment of the side effect of constipation by administering only slightly increased doses of laxatives. Indeed, the authors note that "there was no significant difference in the number of senna/docusate tablets taken at baseline vs. the number taken by the study's end" (see Lazarus, page 10, first full paragraph). Thus the whole benefit to the patients - the entire motivating factor to replicate

anything that the Lazarus reference teaches - was seen when the oral morphine dose was significantly increased while the laxative(s) dose remained the same or increased only slightly.

Applicants reiterate that it would not be possible to replicate the separate titration of the analgesic and the laxative - in striving to acquire the benefits demonstrated by the Lazarus reference - using the single oral dosage form comprising a laxative and an analgesic. As explained above, regardless of the individual doses of the laxative and the analgesic, doubling or tripling the dose of the analgesic using a single oral dosage that combines a laxative and an analgesic as claimed in the instant application necessarily results in the doubling or tripling of the laxative dose as well. Therefore it would clearly be impossible to use the single oral dosage form claimed in the present application to replicate the treatment described in Lazarus, and summarized in paragraphs a-d above, to gain the benefit of the treatment seen by the authors of Lazarus.

Thus, Applicants' statement that "this non-linear increase in docusate dosage, or even decrease in the docusate dosage, with a corresponding increase in morphine dosage would not have been possible using the single solid dosage form claimed in the instant application that would require a doubling of the docusate dose with every doubling of the morphine dose," does not misconstrue the results of Lazarus. Instead, this statement correctly points out that the benefits to be gained (i.e. the motivation for adopting the methods of Lazarus) were achieved by the use of a dosing scheme that would not be possible using the compositions or methods presently claimed in the instant application.

Applicants further submit that one of skill in the pharmaceutical arts would readily recognize this teaching of Lazarus: the benefits of Lazarus were gained by separately titrating the analgesic and the laxative, and one of skill in the pharmaceutical arts would also readily recognize the inconsistency with the present application: the currently claimed oral dosage forms cannot be used to separately titrate the analgesic and the laxative. Thus, Applicants submit that the Lazarus reference clearly teaches one of skill in the pharmaceutical art away from the use of currently claimed single oral dosage forms towards the use of separately administered -

separately titratable - doses of analgesics and laxatives. That is, review of the Lazarus reference above shows that Lazarus teaches the skilled aritisan away from the claimed invention in the single most material respect of the present invention - the dosage formulation itself.

In light of these remarks in rebuttal of the Examiner's *prima facie* case of obviousness, Applicants respectfully request withdrawl of the Examiner's rejections over Lazarus and the description of Senokot-S® tablets from the drugs.com website.

B. Rejections over Lazarus, drugs.com web site and Kaiko.

The Examiner has rejected Claims 1-4, 8-24, and 28-40 under 35 U.S.C. § 103(a) as being obvious over Lazarus in view of the description of Senokot-S® tablets from the drugs.com website and U.S. Patent No. 6,375,957 (hereinafter "Kaiko").

As an initial matter, the Examiner states that Kaiko teaches the use of acetaminophen and codeine. Applicants note that Claims 1, 8-11 and 26-32, as amended, do not recite the use of either codeine or acetaminophen.

The Examiner explains that Kaiko teaches the use of codeine and other opioids in combination with the non-opioid analgesic acetaminophen and an opioid antagonist. The Examiner states that Lazarus teaches "the administration of a single solid dosage form comprising an opioid analgesic and at least about 50 mg of docusate." The Examiner argues, therefore, that one of skill in the art would have been motivated to add acetaminophen to that dosage form or to use codeine as the opioid in the single solid dosage form of Lazarus.

As described earlier with respect to the Examiner's rejection over Lazarus, Lazarus does not teach the formulation and administration of a single solid dosage form. Instead, as elaborated on above, Lazarus teaches away from the use of a single solid dosage form and towards to the use of separate, individually titratable formulations of an analgesic and laxatives. Thus, Applicants submit that the combination of Lazarus, the drugs.com website and Kaiko do not render obvious the single oral dosage formulations recited in the presently pending claims. Further, because Lazarus teaches away from the use of a single oral dosage form and towards the administration of

separate formulations to achieve the benefits of the combined analgesic/laxative therapy studied by the Lazarus authors, there is no reasonable expectation of success in combining or substituting acetaminophen or codeine in the compositions of the instant claims to reap the benefits ot the patients described in Lazarus. Therefore, Lazarus teaches away from the use of the compositions of the present invention and there is no reasonable expectation of success based on the Lazarus research to combine the teachings of Lazarus and Kaiko, and Applicants submit that the obviousness rejection based on this combination of references should be withdrawn.

C. Rejections over Lazarus, drugs.com web site, Kaiko, Colliopoulos and Kais.

The Examiner has rejected Claims 1-4, 8-24, and 28-40 under 35 U.S.C. § 103(a) as being obvious over Lazarus, the description of Senokot-S® tablets from the drugs.com website and Kaiko in view of U.S. Patent No. 5,232,699 (hereinafter "Colliopoulos") and U.S. Patent No. 5,516,524 (hereinafter "Kais").

As an initial matter, the Examiner states that Colliopoulos and Kais teach psyllium to be an effective laxative. Applicants submit that Claims 8, 9, 12-20, 28, 29 and 33-40, as amended, do not recite the use psyllium. Additionally, Applicants note that Claims 6 and 7 specifically recite the use of psyllium in the single oral dosage form of the present invention and therefore, Applicants have assumed that Claims 6 and 7 are included in the Examiner's rejection under the combination of references including the Colliopoulos and Kais references.

The Examiner notes that Colliopoulos and Kais teach combinations of docusate and psyllium in food products or encapsulated compositions having a laxative effect. Thus, the Examiner argues, it would have been obvious to substitute psyllium for senna granules in the Senokot-S® capsules used in the Lazarus study and to combine all of the ingredients - morphine or another opioid, docusate, psyllium and possibly acetaminophen as well - in a single oral dosage formulation. But, as described in detail above, Lazarus does not teach the use of a single oral dosage formulation to administer an opioid and a laxative. Instead, Lazarus teaches away from this invention and towards the separate administration of an analgesic and laxatives. Indeed,

given the teachings of Lazarus and benefits seen with the cancer patients in that study as well as the laxative effects described in Colliopoulos and Kais, one of skill in the art would have been motivated to use the food products of Colliopoulos or the encapsulated formulation of Kais as a substitute for the Senokot-S® capsules used in the Lazarus study to separately administer a combination of docusate and psyllium and a controlled release morphine sulfate oral formulation. Thus, the combination of Lazarus, the drugs.com website, Kaiko, Colliopoulos and Kais teaches the use of separate formulations that are precisely inapposite to the single oral formulations claimed in the instant application.

Therefore, the combination of Lazarus, the drugs.com website, Kaiko, Colliopoulos and Kais teaches away from the use of the compositions of the present invention and Applicants submit that the obviousness rejection based on this combination of references should be withdrawn.

Objections to the Claims

The Examiner has objected to Claims 7 and 8 as containing a misspelling of the word psyllium. Applicants note that this misspelling appeared in Claims 6 and 7, which have been amended herein to correct the misspelling.

Based upon the foregoing, Applicants believe that all pending claims are in condition for allowance and such disposition is respectfully requested. In the event that a telephone conversation would further prosecution and/or expedite allowance, the Examiner is invited to contact the undersigned.

Respectfully submitted,
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